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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/673,380	09/30/2003	Takashi Nakagawa	031729	4353

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EXAMINER	
WEGERT, SANDRA L	
ART UNIT	**PAPER NUMBER**
1647	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/07/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/673,380	NAKAGAWA ET AL.	
	Examiner	Art Unit	
	Sandra Wegert	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) *6* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/30/03, 5/24/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

The Information Disclosure Statement, received 30 September 2003, and the Information Disclosure Statement, received 24 May 2004 have been entered into the record.

It is noted that citations crossed off by the examiner have been cited in duplicate.

Applicant's election of Invention I (Claims 1-5) in the Paper of 8 November 2006 is acknowledged. Applicant also elected additional Inventions as follows: *rapidly progressive glomerular nephritis syndrome* and *Par-2 ligand.* The election was made without traverse. The Restriction requirement is deemed proper and is therefore made final.

Claim 6 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Invention, there being no allowable generic or linking claim.

Claims 1-5 are under examination in the Instant Application.

Informalities

Specification-

The disclosure is objected to because of the following informalities: Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows: A reference to the prior application must be inserted as the first sentence of the specification of this application or in an application data sheet (37 CFR 1.76).

Appropriate correction is required.

Claim Rejections

Claim Rejections - 35 USC § 112, first paragraph - enablement.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification is not enabling for the limitations of the claims wherein a kidney disease is prevented or treated by administering a PAR-2 activating agent to a patient.

The claims are directed to methods of preventing or treating kidney diseases, specifically rapidly progressive "glomerulo nephritis" (usually spelled "glomerulonephritis") syndrome, by administering a composition containing the PAR-2 ligand (SLIGKV).

The issue of "preventing" kidney diseases is addressed below. As far as *treatment* of rapidly progressive glomerulonephritis syndrome or other kidney diseases, the specification discloses methods of correcting one symptom of an experimental nephritis in mice. An immune reaction had been generated in the animals by injecting antibodies against the glomerular basement membranes (Specification, p. 9 and Figure 1). The mice developed a severe nephritis based on the presence of large amounts of albumin in their urine. In other words, the severe autoimmune reaction resulted in destruction of the glomeruli and subsequent "leakiness" of the kidney nephrons over the course of several weeks (Figure 1). The applicants also demonstrated

that administration of the presumed PAR-2 peptide ligand in the mice with the artificial glomerulonephritis partially reversed the particular symptom of high urine albumin (Figure 5).

In In re Wands, 8USPQ2d, 1400 (CAFC 1988) page 1404, the factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Claims 1-5 encompass methods for treating kidney diseases by administering a PAR-2 ligand. The specification teaches adding the mouse SLIGRL peptide to animals with an experimentally-induced nephritis. However, no attempt was made to associate naturally-occurring "kidney diseases" in patients (humans) with PAR-2. There is no evidence from the literature, and no experimental evidence from the instant Specification that PAR-2 plays a role in any kidney diseases, including the one that was produced experimentally in mice.

The experimentally-induced glomerulonephritis in the instant Specification was likely produced by a mechanism not involving PAR-2. Indeed, the animals in which an experimental glomerulonephritis was generated were PAR-2 knockouts. This argues against PAR-2's involvement in the experimental glomerulonephritis, since the knockout mice still developed glomerulonephritis. In addition, one cannot generalize between animal experiments which used PAR-2 knockouts to produce a glomerulonephritis and a kidney disease which may occur in human patients. In fact, others have pointed out that PAR-2 knockout animals, if they survive very early development, are phenotypically-normal, indicating that PAR-2 probably plays a

minor role in adult kidney physiology (Rondeau, et al, 2001, Nephrol. Dial. Transplant., 16: 1529-1531, p. 1529, paragraph 4).

In addition, administration of peptides (presumably to blood) is not reliable compared to administration of more stable non-peptidic small molecules. Proteases abound in many tissues (Gee, et al, 1985, Biochem., 228: 119-126) limiting peptide effects in blood and muscle, for example, to minutes or seconds; the peptide must then pass to the kidney to presumably have an effect.

Due to the large quantity of experimentation required to determine how to treat kidney diseases by administering a PAR-2 ligand; the lack of direction as to treatment of any naturally occurring kidney diseases or any naturally-occurring glomerulonephritis; the lack of working examples in which a glomerulonephritis was treated in animals that had functioning PAR-2 receptors; the state of the art showing the complexity of kidney diseases; the state of the art that shows PAR-2 knockout animals are phenotypically-normal (e.g., have normal kidney function); and the breadth of the claims which embrace methods of treating many kidney diseases, many of which might have different underlying etiologies-- undue experimentation would be required of the skilled artisan to make and use the claimed invention in its full scope.

Furthermore, the specification does not disclose preventing any kidney diseases by administering PAR-2 ligands. The term "prevent" is interpreted as meaning that an activity will not occur, i.e. kidney diseases will not occur. Undue experimentation would be required of the skilled artisan to determine the quantity of PAR-2 ligand to be administered, the best route of

administration, the duration of treatment, and any possible side-effects to prevent any kidney diseases from occurring.

35 USC § 112, first paragraph – Written Description.

Claims 1-5 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-5 are directed to methods of treating kidney diseases by administering a PAR-2 ligand. Furthermore, the claims recite use of a PAR-2 ligand [polypeptide], a PAR-2 ligand derivative, trypsin, tryptase, tissue factor/VIIa factor, Xa factor, acrosin, or trypsin-like serine protease for use in a method to treat kidney diseases.

The specification teaches the mouse PAR-2 ligand polypeptide (SLIGRL). However, the specification does not teach functional or structural characteristics of all PAR-2 activating agents used for the claimed methods. The description of one polypeptide is not adequate written description of an entire genus of functionally equivalent polypeptides or other non-peptide ligands. In addition, the recited PAR-2 ligands in claim 5 are better known as PAR-1 ligands (Rondeau, et al, 2001) and have not been confirmed to be PAR-2 ligands.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of

ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

With the exception of the peptide referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed PAR-2 activating agents, and therefore, would not know how to use them. Conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of use. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of use. The ligand itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only a polypeptide comprising the amino acid sequence: SLIGRL, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Conclusion:

Claims 1-5 are rejected for the reasons cited above.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (571) 272-0895. The examiner can normally be reached Monday - Friday from 9:00 AM to 5:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Brenda Brumback, can be reached at (571) 272-0961.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

29 January 2007

SLW

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